CONFERENCE ON ARTERIAL HYPERTENSION: DIAGNOSIS AND MANAGEMENT*

General Discussion, Morning Session

DAVID S. BALDWIN, *Moderator*

Associate Professor of Medicine
New York University School of Medicine
New York, N. Y.

Discussants

JAMES C. HUNT
ARTHUR C. GUYTON
CAROLINE B. THOMAS
KARL ENGELMAN

DR. BALDWIN. Dr. Hunt, how do you identify a pressor kidney in unilateral pyelonephritis? How do you deal with the hypertensive patient who has a small kidney with normal major renal arteries?

DR. HUNT. Unilateral atrophic pyelonephritis with a urographically normal contralateral kidney is a most uncommon situation in hypertensive patients. Far more often there is some evidence of calyceal distortion or even significant renal atrophy in the contralateral kidney. When the contralateral kidney is of normal size and without evidence of major calyceal damage, it is worthwhile to proceed with a more detailed investigation to determine whether the atrophic kidney is causative of hypertension. We ordinarily investigate by isotope renography and renal arteriography and in the absence of a demonstrated renal arterial lesion, we proceed with differential renal-function studies and renal venous renin-activity determinations. In other words the investigation does not differ from that in cases of suspected renovascular hypertension if the patient is otherwise a suitable surgical candidate. On occasion, the atrophic kidney is proved to be a "pressor" kidney by renin-activity levels greater than those in the contralateral kidney; however, it is far more likely that functional significance will be demonstrated by the differential renal-function studies. Characteristically, with functionally significant lesions the urinary volume is diminished by 50%

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or more, and the concentrations of sodium, reabsorbable solute, inulin, and PAH are essentially equal, but usually reabsorption of sodium and water is diminished in the kidney with the lesion—commonly referred to as a "salt- and water-losing kidney." When such functional changes are demonstrated and when the contralateral kidney has a normal or near normal PAH clearance, we have generally obtained marked improvement or total relief of associated hypertension by removal of the atrophic kidney.

Our management of patients with a kidney that is small but normal arteriographically is similar to that described above for patients with apparent dominant unilateral atrophic pyelonephritis. Unless physiologic evidence of a functionally significant lesion can be demonstrated by renin-activity determinations from the renal venous blood or from differential renal-function studies, nephrectomy is seldom followed by relief of associated hypertension.

DR. BALDWIN. Dr. Guyton, will you comment on the relevance of your experimental and computer model to the pathogenesis of essential hypertension?

DR. GUYTON. The importance of the computer model in relation to essential hypertension is that it emphasizes probable involvement of the kidneys in this disease. Specifically, the model shows that if the kidneys were functioning entirely normally, the high arterial pressure by itself would cause diuresis, and this in turn would decrease the pressure back to normal. Therefore, if hypertension is to be maintained the kidneys must require a higher-than-normal arterial pressure to make them excrete normal amounts of water and salt. The abnormality that causes this could be primarily in the kidney itself, as increased afferent arteriolar resistance or excessive tubular reabsorption of salt and water. Or the primary abnormality could be extrarenal but acting on the kidney to cause its abnormal retention of salt and water. If this is true, one would think especially of humoral factors that originate in other parts of the body but that affect kidney function. Yet, most important of all, the computer analysis suggests that normal renal output can occur only at high arterial pressures in essential hypertension and that this effect must be involved in the genesis and maintenance of the hypertension.

DR. BALDWIN. The next question is for Dr. Thomas. Relative to the question of whether vascular disease is caused by or is simply re-

lated to hypertension as an associated inherited trait: are there data on the incidence of vascular disease in the normotensive family members of individuals with hypertension?

DR. THOMAS. The only data bearing on this question that I know of come from our own family history studies. Using 266 medical students as probands, we examined the interrelation of hypertension and coronary disease in the parents, aunts, and uncles of the probands.* The siblings of hypertensive parents had significantly more 1) hypertension, and 2) hypertension or coronary disease than the siblings of normotensive parents. Regarded independently, the prevalence of coronary disease among the siblings of hypertensive parents was not significantly different than the prevalence among the siblings of normotensive parents (5.0% vs. 4.2%). When the siblings who had coronary disease combined with hypertension are subtracted from the total siblings with coronary disease, however, a suggestive difference appears: 3.9% of the 181 siblings of hypertensive parents had coronary disease without hypertension compared to 1.0% of the 1,272 siblings of normotensive parents. This was an early study, when the numbers involved were relatively small. The work should be repeated, now that we have a much larger population to analyze.

DR. BALDWIN. The next question is for Dr. Engelman. What are the course and consequences of hypertensive disease associated with pheochromocytoma? Do renal arteriosclerosis, cerebral thrombosis, or coronary thrombosis occur?

DR. ENGELMAN. It is our clinical impression that patients with hypertension secondary to pheochromocytoma generally tend to have less vascular disease and, especially, renal disease than other hypertensives. Intracranial hemorrhage and myocardial infarction is not rare, however, especially in the older group. In addition one sees at times an unusual cardiomyopathy which results in severe congestive failure. This problem seems to be more related to a defect in myocardial metabolism than to severe hypertension since we have observed severe cardiomyopathy in two patients with nearly normal blood pressure who later responded to medical and surgical therapy.

DR. BALDWIN. Dr. Guyton: Will you comment on the relevance of your experimental and computer model to the pathogeneses of hy-

*See Table 9 in Thomas, C. B. and Cohen, B. H. The familial occurrence of hypertension and coronary artery disease, with observations concerning obesity and diabetes. *Ann. Intern. Med.* 44:90, 1955.

pertension in pheochromocytoma, aldosteronism, and renal artery stenosis?

DR. GUYTON. Both aldosteronism and bilateral renal artery stenosis are known to shift the renal function curve to the right, that is, so that the kidneys require greatly increased arterial pressure to excrete normal amounts of salt and water. Therefore it would be expected that the arterial pressure should be greatly increased when the system reaches equilibrium. These shifts of the renal function curves were illustrated in Figure 3 of my paper and the ensuing development of hypertension was discussed also in the paper. However the situation is much more complex for unilateral renal artery stenosis. Theoretically, any rise in arterial pressure induced by the stenotic kidney should cause the opposite kidney to diurese and lower the pressure most of the way back toward normal *unless* the stenotic kidney should send some signal to the opposite kidney to make it also retain salt and water. This signal could be in the form of angiotensin acting directly on the opposite kidney to cause vascular constriction or acting indirectly by increasing the secretion of aldosterone which, in turn, affects the opposite kidney.

In pheochromocytoma, it is always a temptation to say that hypertension is caused entirely by the generalized vasoconstriction induced by the catecholamines. Undoubtedly the acute episodes of elevated pressure are caused by this effect. However the sustained elevation of pressure would require some effect that would keep the kidneys from diuresing when the pressure is elevated because diuresis theoretically would lower the pressure back toward normal. It happens that the catecholamines do greatly increase renal afferent arteriolar resistance and thereby reduce renal output. On this basis the model predicts that the sustained elevation of arterial pressure results from the renal effects of the catecholamines rather than from the generalized vasconstrictor effects elsewhere in the body.

In summary, the model emphasizes the extreme importance of the kidneys in almost all types of hypertension. Unless the kidneys have something that causes them to retain salt and water, any type of hypertension would cause the kidneys to dehydrate the body until the arterial pressure should return to normal. Therefore the model predicts that the kidneys almost have to be affected in some way, either directly or indirectly, in all types of chronic hypertension.

DR. BALDWIN. Dr. Hunt, will you comment on your experience with renin levels as an aid to the diagnosis of renal hypertension? What are the renin levels in patients with bilateral renal-artery stenosis?

DR. HUNT. As outlined in the text of my paper and in its Table V, we have found the measurement of renin activity in the inferior vena cava and in both renal veins in appropriately prepared patients (those without antihypertensive medication for at least two weeks and those prepared by sodium restriction and administration of thiazide diuretics and maintained in the upright position for four hours prior to venous sampling) a valuable procedure in the diagnosis and the selection of patients with renal-artery lesions for surgical management.

Renin-activity levels on the involved or more severely involved side should exceed those in the contralateral renal vein by 50% or preferably by 100% or even more when the lesion is functionally significant. However it is worthy of note that on occasion we have studied patients with curable renovascular hypertension who had essentially equal and normal renin activity in the renal veins, only to find a functionally significant lesion by differential-renal function studies. If renal-artery repair is surgically feasible under such circumstances, it can produce marked amelioration or relief of hypertension. But nephrectomy should be considered with extreme caution under these circumstances, since the surgical result may well be dictated by the functional integrity of the contralateral kidney.

Renin-activity levels in patients with bilateral renal-artery stenosis are more difficult to evaluate. In the absence of malignant hypertension, a ratio of 1:1.5 or greater between the kidneys usually indicates a functionally significant lesion. However surgical intervention probably should be predicated primarily on the basis of differential renal-function studies, since the renal management of salt and water—and thus the concentration of nonreabsorbable solute such as inulin or PAH—will indicate more accurately the probability of surgical relief of elevated blood pressure.

DR. BALDWIN. I shall ask the last question of Dr. Engelman. What is the nonsurgical management of pheochromocytoma, as in patients with malignant tumors?

DR. ENGELMAN. Medical therapy for patients with pheochromocytoma has an important role not only for cases with malignancy but also for preoperative preparation. Therapy may be carried out either with

adrenergic blocking drugs or with the currently experimental drugs which block the tumor synthesis of the catecholamines. In the former group are the alpha adrenergic blocking drug, phenoxybenzamine (dibenzyline), and the B-adrenergic blocker, propranolol. The inhibitor of catecholamine synthesis with which we have the greatest experience is alpha-methyltyrosine.